REMARKS

Claims 1-62 have been canceled, and claims 63-69 have been added. The added claims are fully supported by the original claims and the specification.

In the November 15, 2007, Office Action, claims 34 and 38 were objected to for an informality. Claims 29 and 41 were rejected under 35 USC § 112, first paragraph, for lack of enablement. Claim 35 was rejected under § 112, second paragraph, as indefinite. Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 were rejected under 35 USC 103(a) as obvious over McSwiggen and Tuschl. Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 were rejected under 35 U.S.C. § 103(a) as obvious over Cook, Damha and Tuschl. The specific grounds for rejection, and applicants' response thereto, area set forth in detail below.

Support for amendments

The added claims are fully supported by the specification and original claims. Specifically, claim 63 is supported at page 6, line 29, page 23, line 10, page 24, lines 17-23, page 25, lines 4-13, Figure 2B, Figure 12B, and original claims 11-13 and 15. Claim 64 is supported at page 6, line 29. Claim 65 is supported at page 4, line 9 and page 6, lines 23-30. Claims 66 and 67 are supported at page 6, lines 25-30, and in Figure 12B. Claim 68 is supported at page 6, line 29. Claim 69 is supported at page 2, lines 27-28, page 3, lines 6-8, page 6, lines 3-5, Figure 12B, and original claims 1 and 4.

Rejection Under 35 U.S.C. §112

Claims 29 and 41 are rejected under 35 USC § 112, first paragraph, for lack of enablement. Claim 35 is rejected under § 112, second paragraph, as indefinite. Specifically, the Examiner asserts that the language "pharmaceutical composition" as recited in claims 29 and 41 "implies" a therapeutic or treatment benefit that allegedly is not enabled. Claims 34 and 38 are rejected due to alleged informalities. Applicants respectfully traverse.

As the Examiner correctly notes, claims 29 and 41 are directed to compositions and not methods. It is axiomatic that the "enablement requirement is met if the description enables any mode of making and using the invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). The compositions of claims 29 and 49 can be

used *in vitro* regardless of their "implied" use in methods of treatment. This use of the claimed compositions is fully enabled by the working examples provided in the instant specification. Accordingly, the claims are fully enabled and the rejection should be withdrawn.

In any event, claims 29, 34, 38 and 41, have been canceled and, accordingly, the rejections are moot.

Rejections Under 35 U.S.C. §103(a)

Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 were rejected under 35 USC 103(a) as obvious over McSwiggen and Tuschl. Claims 12-13, 15-17, 19, 29, 31-32 and 34-62 were rejected under 35 U.S.C. § 103(a) as obvious over Cook, Damha and Tuschl. The rejections are addressed below in the order set forth in the Office Action.

McSwiggen and Tuschl

The Examiner asserts that McSwiggen (US Patent Application US2003/0190635) teaches a chemically modified 19-25 nucleotide dsRNA capable of silencing expression of a target gene. The dsRNA may be modified at one or more nucleotides using various types of chemical modification, including modifications to the ribose sugar, the base and/or the phosphate backbone, either on one or both strands. Tuschl is cited as teaching blunt ended dsRNA that can induce RNA interference and also the use of modified nucleotides. The Examiner asserts that in light of these references it would have been obvious to make a dsRNA molecule comprising 2' modified nucleotides, and it would also have been obvious and "a matter of routine experimentation" to arrange 2'- modifications in any dsRNA molecule so as to provide maximum stability and functionality.

Moreover, the Examiner alleges that the references would have motivated one of ordinary skill in the to "test all possibilities and configurations" of 2' modified and unmodified nucleotides in one or both strands because it was well known that such modifications, "impart increased stability and functionality in any RNA molecule." The Examiner further relies on *In re Aller*, (220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)) for the proposition that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Finally, the Examiner asserts that

there is a finite number of ways to configure 2' modified and unmodified nucleotides "known" to increase stability and functionality in dsRNA, and that there would have been a reasonable expectation of success in identifying dsRNA having an alternating pattern of 2' modified and unmodified nucleotides on one or both strands of RNA "from the finite number of possible modifications of a dsRNA taught by Tuschl et al. that retain RNAi activity."

Applicants respectfully traverse because there was no motivation in the art to prepare a nucleic acid having the 2'-O-methyl modifications recited in the instant claims. There was also no reasonable expectation that the 2'-O-methyl modifications recited in the claims would provide a nucleic acid that would either retain RNAi activity or increase stability, let alone both increase stability and maintain activity. Moreover, the instantly claimed nucleic acids have the unexpected property of having both a remarkable increase in stability and high degree of functional activity in promoting gene silencing. For at least these reasons, applicants respectfully submit that the rejection is improper and should be withdrawn.

A. McSwiggen is not available as prior art

McSwiggen has a filing date of 25 July 2002 and claims priority to provisional applications 60/358,580 (filed February 20, 2002), 60/363,124 (filed March 11, 2002), and 60/386,782 (filed June 6, 2002). McSwiggen was not published until 9 October 2003. The earliest filing date of the instant application is 5 August 2002. Accordingly, because McSwiggen was not published until after the earliest priority date of the instant application, it is available as a reference only under 35 USC § 102(e) and may properly be antedated by an appropriate evidentiary showing of prior invention.

The declaration by the inventors pursuant to 37 CFR § 1.131 (appended hereto as EXHIBIT A) clearly demonstrates that the captioned application was conceived and reduced to practice prior to McSwiggen's earliest priority date and therefore prior to the effective prior art date of McSwiggen. Accordingly, McSwiggen is not prior art against the instant application and all rejections based on McSwiggen should be withdrawn.

B. The Examiner has misread the disclosures of McSwiggen and Tuschl

The Examiner admits that McSwiggen fails to teach a dsRNA having alternating 2'-modified and unmodified nucleotides linked by a phosphodiester bond. The Examiner also admits that Tuschl fails to teach the number and placement of 2'-modified nucleotides such that siRNA activity is retained, and does not specifically teach a siRNA comprising an alternating pattern of 2' modified and unmodified oligonucleotides. However, the Examiner asserts that Tuschl teaches that "more extensive" 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Applicants respectfully submit that neither McSwiggen nor Tuschl disclose so much as the Examiner supposes.

(i) McSwiggen fails to disclose dsRNA molecules containing any pattern of modifications

Specifically, McSwiggen does not teach or suggest any pattern of 2'-O-methyl modified nucleotides that can both increase the stability of a dsRNA and retain RNAi activity. Indeed McSwiggen fails to teach or suggest any pattern of 2'-O-methyl modified nucleotides of a dsRNA that retains RNAi activity. Nor does McSwiggen teach or suggest any pattern of 2'-O-methyl modified nucleotides that will increase stability of a dsRNA. In fact, McSwiggen does not teach or suggest a dsRNA containing any pattern of 2'-O-methyl modified nucleotides whatsoever. In addition, McSwiggen fails to teach or suggest any specific 2'-O-methyl modifications spanning the antisense strand that will increase the stability of a dsRNA, let alone increase stability while simultaneously retaining functionality.

The Examiner states that "...the chemical modifications of dsRNA as taught by McSwiggen [are] capable of improving cellular uptake and stability of dsRNA." Applicants respectfully submit that this statement ignores the key question of whether or not the modifications eliminate the ability to elicit RNAi. A non-functional molecule might in theory be more stable and better taken up by a cell than a functional molecule, but it will still be non-functional because it will fail to elicit RNAi. Thus, any teaching or suggestion regarding modifications that may or may not stabilize a dsRNA molecule or increase its cellular uptake is insufficient to present a *prima facie* case of obviousness here without an additional teaching of the relationship between the chemical modifications effect on stability and activity. McSwiggen contains no such teaching.

(ii) Tuschl fails to teach any 2'-O-methyl modified dsRNA molecules that retain RNAi activity

Tuschl (WO 02/44321) is cited as teaching 19-25 nucleotide dsRNA molecules, modified at the 2'-position of the ribose sugar, that are capable of mediating degradation of homologous RNAs and the use of modified nucleotides. The Examiner admits that Tuschl does not teach the number and placement of 2'-modified nucleotides such that siRNA activity is retained and also does not specifically teach an siRNA comprising alternating pattern of 2'-modified and unmodified oligonucleotides.

Applicants respectfully submit that the Examiner has misread several aspects regarding the teachings of Tuschl. First, the Examiner asserts that Tuschl teaches that "modifications of the entire double stranded RNA with 2'-O-methyl or 2'-O-deoxy is not well tolerated." The phrase "not well tolerated" suggests activity is reduced but not eliminated. However, Tuschl . teaches that such modifications actually completely abolish RNAi activity (page 46, lines 13-14).

Second, the Examiner asserts that Tuschl teaches that dsRNA comprising eight 2'-O-methyl modified nucleotides had RNAi activity and that fully modifying all 42 nucleotides with 2'-O-methyl abolished RNAi activity. While it is correct that complete modification with 2'-O-methyl abolishes RNAi activity, Tuschl does not teach a dsRNA comprising eight 2'-O-methyl modified nucleotides that has RNAi activity.

Third, the statement by the Examiner that "Tuschl et al. clearly recognizes and teach that 2'-modifications enhance the nuclease stability of siRNA molecules and that more extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi" could be miscontrued in two important ways. The statement first implies that Tuschl demonstrates a 2'-O-methyl modified dsRNA with increased stability. This is not correct. Tuschl describes no 2'-O-methyl modified dsRNA other than fully 2'-O-methyl modified dsRNA, which is completely inactive. By using the term "reduce" the statement secondly implies that extensively 2'-O-methyl- or 2'-deoxy-modified dsRNA retains some activity. The only extensively 2'-O-methyl or 2'-deoxy modified dsRNA taught by Tuschl is fully modified dsRNA and Tuschl clearly and dispositively states that "[c]omplete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did substitution by 2'-O-methyl residues" (page 46, lines 13-14). A fairer reading of Tuschl, therefore, would be that more extensive 2'-O-methyl modification would be expected to eliminate, rather than merely reduce, RNAi activity.

Fourth, the Examiner states that "Tuschl et al. do not explicitly teach the optimum number and placement of 2'-sugar modifications such that siRNA activity is retained...." The term "optimum" as used here implies that Tuschl somehow teaches multiple 2-O-methyl modified dsRNAs with varying degrees of activity. However, with respect to 2'-O-methyl modified dsRNA, the only actual example provided by Tuschl is completely inactive. Tuschl prophetically suggests modifying the ends of a dsRNA to stabilize the molecule but does not teach what level of activity is retained by these molecules. More particularly, however, Tuschl does not teach placement of 2'-O-methyl groups anywhere in the middle region of a dsRNA in a manner that retains RNAi activity.

C. *McSwiggen recognizes the deficiencies in the art but fails to remedy those deficiences*

The Examiner alleges that one of ordinary skill in the art would have been motivated to "test all possibilities and configurations of 2'-modified and unmodified nucleotides in one or both strands because it was well known that modifications, such as 2'-O-methyl modifications, "impart increased stability and functionality in any RNA molecule." Applicants address the practical impossibility of this assertion in detail below, but first point out that the Examiner's statement serves to make that point that neither McSwiggen nor Tuschl, alone or in combination, point one of skill in the art to the claimed invention. If either of the two references, either alone or in combination, provided any guidance or direction to one skilled in the art to the claimed invention, then one would *not* have been motivated to make each and every possible combination of modifications.

Specifically, McSwiggen fails to teach or suggest how to use 2'-O-methyl modifications that both impart both increased stability and functionality in terms of mediating the cleavage of target mRNA. As stated above, a non-functional dsRNA, i.e., a dsRNA that is unable to mediate RNAi, but that has increased stability and increased cellular uptake, is still non-functional.

Moreover, McSwiggen explicitly acknowledges in paragraph [0006] the well known facts that the prior art, in referring, in part, to 2'-O-methyl modifications on a dsRNA "fails to show to what extent these modifications are tolerated in siRNA molecules nor do they provide any examples of such modified siRNA." McSwiggen likewise fails to show to what extent these modifications are or are not tolerated in siRNA molecules nor does it provide any data describing

results obtained with such modified siRNA. In other words, McSwiggen recognizes the limitations of the prior art yet nothing in McSwiggen would have made one of ordinary skill in the art any the wiser with respect to those limitations. Without a teaching or suggestion of how to place 2'-O-methyl modifications on a dsRNA, particularly across the antisense strand, in a manner that would both increase stability and retain activity, there would have been no motivation to make the claimed invention and no reasonable expectation of success.

D. Nothing in either McSwiggen or Tuschl would have motivated one of ordinary skill in the art to make 2'-O-methyl modified dsRNA having the pattern recited in the claims

There is simply no connection between the modifications of McSwiggen and those of the present invention. Tuschl provides no teaching that would remedy this lack of connection. The modifications of the present invention are based simply on the order of the nucleotides in a dsRNA molecule and are arranged such that an alternating pattern of modifications is formed. By contrast, McSwiggen relates to modifications based on the chemical identity of each nucleotide in a dsRNA molecule, not the order in which the nucleotides appear in that molecule More specifically, McSwiggen teaches modification of pyrimidines. By way of background, RNA is made up of 4 different types of nucleotides, A, G, C and U. Two of these, A and G, belong to the chemical class of nucleotides called purines. The other two, C and U, belong to the chemical class of nucleotides call pyrimidines. Each dsRNA molecule will have a different sequence, or arrangment, of each of the A, G , C and U nucleotides, based on the sequence of the target mRNA. Thus, the placement of McSwiggen's modifications will change with essentially every sequence chosen without any reference to the order of each nucleotide in the sequence and without any regard to the formation of any specific pattern of modifications. In light of this one of ordinary skill in the art would not have been motivated to make modifications based on any pattern but, at most, would have tried modifications based on the specific chemical identity of each base.

E. There was no motivation in the art to make the claimed dsRNA molecules: The state of the art at the time of the invention

The rejection also relies upon a misrepresentation of the state of the art at the time the invention was made. Thus, the Examiner asserts that McSwiggen stands for the proposition that

modified ribonucleotides can be used to stabilize dsRNA molecules and that Tuschl teaches that "more extensive" 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Based upon these assertions, the Examiner alleges that the instantly claimed molecules were merely "optimized" and obvious variants of those molecules allegedly taught by McSwiggen and Tuschl. However, the Examiner reads far more into the references than is there, as is shown by the Declaration of Dr. Mike Gait, appended hereto as EXHIBIT B. A proper consideration of the state of the art at the time the present invention was made clearly leads to the conclusion that the instantly claimed molecules are nonovious and therefore withdrawal of the rejection respectfully is requested.

Notably, as Dr. Gait explains, in 2002 the identity and nature of the nucleases that degrade dsRNA was not well understood. There was a further prejudice in the art that exonucleases, rather than endonucleases, were likely to be the primary causes of dsRNA degradation. This prejudice is shown in the nature of the modifications described by Tuschl which focused on modifications at the ends or termini of the dsRNA strands, a classic strategy for inhibiting exonuclease digestion. By contrast, the present inventors surprisingly discovered that endonucleases are primarily responsible for degradation of dsRNA of the type used in RNA interference.

In the only discussion of modifications in the interior of the strand, Tuschl states that a molecule containing a fully 2'-O-methyl modified antisense strand was inactive in causing RNA interference. The Examiner uses this statement to assert that one skilled in the art therefore would somehow have been motivated to use a less extensively modified dsRNA to avoid this loss of activity. However, the Examiner's assertions reflect a lack of understanding of the art at the time the present invention was made, lack factual foundation, and rely completely on prohibited hindsight.

A proper consideration of Tuschl's results would not have led one of ordinary skill in the art to make a less extensively modified dsRNA for RNAi purposes. Rather, the reasonable and scientifically appropriate conclusion would have been to avoid making modifications to the interior of the antisense strand of the dsRNA so as to avoid inhibiting binding of the antisense strand in the RISC complex. Thus, Tuschl describes preparing end-modified molecules that were successful in inducing RNAi, but compares the results of end-modification to the complete loss of activity caused by completely modifying the antisense strand:

The siRNA User Guide

> Efficiently silencing siRNA duplexes are preferably composed of 21-nt antisense siRNAs, and should be selected to form a 19 bp double helix with 2-nt 3' overhanging ends. 2'-deoxy substitutions of the 2-nt 3' overhanging ribonucleotides do not affect RNAi,.but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications, however, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.

See Tuschl at page 49. Contrary to the Examiner's assertions, this does not suggest that there somehow might be some less extensive modification that would be successful at stabilizing dsRNA while mediating RNAi; rather, it is a clear suggestion that modifications *other than* modifications at the termini of the molecules would be expected to inhibit formation of the RISC complex and therefore prevent RNAi activity. Rather than a suggestion to make less extensively modified molecules, it is a clear warning that molecules that are more extensively modified than end-modified dsRNA are unlikely to be active in mediating RNAi. The conclusion that the Examiner draws from Tuschl is not only incorrect, but it is the exact *opposite* of the clear statements made by Tuschl. For at least these reasons, applicants respectfully submit that the rejection is improper and should be withdrawn.

F. McSwiggen fails to overcome the prejudice in the art against 2'O-methyl modifications in the antisense strand.

As described above, McSwiggen is not available as prior art against the instantly claimed invention and therefore McSwiggen cannot cure the many deficiencies of Tuschl. However, even if it were available, nothing in McSwiggen, either alone or in combination with Tuschl, would have led one of ordinary skill in the art to the present invention. More specifically, McSwiggen fails to describe any data showing that molecules having 2'O-methyl modifications in the interior of the antisense strand are active in mediating RNAi.

Thus, McSwiggen speculates that a certain number of nucleotides on each strand of a dsRNA might be 2'-modified by any one of a number of possible modifications, including fluoro and 2'O-methyl groups. The only teaching provided by McSwiggen regarding the placement of these modifications is to suggest modification at pyrimidines. Nothing in McSwiggen teaches or suggests the pattern of 2'-O-methly modified and unmodified nucleotides recited in the instant

claims. More specifically, McSwiggen provides no data that would have overcome the prejudice of one skilled in the art regarding the nature of modifications that should be avoided in preparing dsRNA for RNAi applications.

As explained by Dr. Gait, the prejudice in the art in 2002 was that modification of the antisense strand of dsRNA molecules by larger groups, such as 2'-O-methyl, would cause steric hindrance in the RISC complex that would inhibit or prevent RNAi activity. McSwiggen provides a large table of single stranded RNA molecules that contain various modifications, but provides precious little data regarding activity of these molecules. Moreover, although McSwiggen's table shows a very small number of 2'-O-methyl modified antisense strands, no data are shown for either the stability or RNAi activity of these strands. The only data shown by McSwiggen in which the antisense strand is modified at positions across its entire length are when the modification is 2'-fluoro. It is well known that a fluorine atom is much *smaller* than a hydroxyl group, whereas a methoxy group is clearly *much larger*. It is telling that, when McSwiggen provides data using a modified antisense strand, it is for strands containing the fluoro substituent. The clear conclusion is that McSwiggen is conforming to the prejudice in the art in 2002 – namely, that large substituents should be avoided in the center of the antisense strand.

Finally, any reasonable review of McSwiggen would convince one of ordinary skill in the art that the Examiner's position that mere "routine experimentation" is all that is required to obtain the instantly claimed compounds, even if legally relevant, is factually unfounded. McSwiggen shows literally hundreds of RNA sequences that purport to be useful for mediating RNAi (albeit with little actual data). Why, then, does McSwiggen fail to describe a single molecule that remotely resembles the instantly claimed molecules? If the instantly claimed molecules can be obtained by mere optimization of known molecules, why did McSwiggen fail to obtain such molecules? The answer of course is that the present invention is directed to molecules that are not taught or suggested by the prior art and that could not have been obtained by "routine experimentation." Accordingly, withdrawal of the rejection respectfully is requested.

G. The Examiner's assertions regarding a finite number of possible modifications of dsRNA molecules are improper

The Examiner makes the remarkable statement that one would have been motivated to test "all possibilities and configurations of 2' modified and unmodified nucleotides in one or both strands" because it was well known that such modifications "increased stability and function in any inhibitor nucleotides, such as a dsRNA." This statement misapplies the relevant law and evinces a failure to properly consider the factual background of the instant invention.

As shown in the accompanying declaration by Dr. Jörg Kaufmann, appended hereto as EXHIBIT C, there are approximately 10^{17} or 100,000,000,000,000,000 possible ways of arranging 2'modified and unmodified nucleotides on antisense and sense strands of a dsRNA 23 nucleotides in length. This number assumes the dsRNA contain no modifications other than 2'-O-methyl modified nucleotides. The number therefore does not even take into account the possibility of including other possible 2'-modifications taught by McSwiggen which includes groups where the 2'-OH is substituted with H, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, and substituted silyl modifications. When these possibilities are included the number of possible arrangements becomes unimaginably high. In light of these numbers it is clear that the "routine" testing proposed by the Examiner is impossible and the rejection relies on a grossly mistaken factual premise.

Moreover, it appears that the legal basis for the rejection relies on the recent *KSR* case, since the Examiner's reference to a "finite" number of possibilities closely follows the language in that case. See 82 USPQ2d 1385 (2007). The Examiner misapplies the teachings of that case however.

In KSR the Supreme Court states that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

(Emphasis supplied). Thus, in the very special case where there are a knowable and reasonable number of *indentified* and *predictable* solutions then it might be that the solutions are obvious. For example, if there are 10 ways of arranging a brake pedal and the results of those arrangements are predictable, then the *KSR* cases concludes that each one of the 10 arrangements is *prima facie* obvious.

The instant case could not be more different from the situation contemplated in KSR. Here, the results of modifying a dsRNA molecule are not predictable, and the nature and placement of the modifications has not been identified in the art. In the absence of any identified and predictable solutions, the *KSR* analysis described above simply is inapposite and the rejection is improper and should be withdrawn.

H. There was no reasonable expectation of success in making the claimed dsRNA molecules

As described above, all that was known in the art at the time that the present invention was made was that modifying the terminus of a dsRNA did not abolish RNAi activity, while complete modification of the antisense strand did abolish that activity. Nothing in the art would have led of ordinary skill in the art to conclude that a dsRNA having the structure recited in the instant claims would be highly active in mediating RNAi while showing significant stability against degradation. In the absence of any reasonable expectation of success, no *prima facie* case of obviousness exists, and the rejection should be withdrawn.

I. The claimed compounds have unexpected properties

For the reasons set forth above, the Examiner has failed to set forth a *prima facie* case of obviousness against the instantly claimed invention. However, even if it is assumed, purely for the sake of argument, that a *prima facie* exists, it is rebutted by the unexpectedly superior results shown by the claimed invention. In particular, nothing in the art taught or suggested that is was possible to prepare modified dsRNA molecules that retain high RNAi activity while providing high stability against nucleases *in vivo*.

The decaration by Dr. Klaus Giese, appended hereto as EXHIBIT D, describes results that show that dsRNA molecules having the structure recited in the instant claims are both highly

active and stable in serum. Moreover, this result is a general one that has been demonstrated in dsRNA molecules directed against over 100 gene targets.

Accordingly, applicants respectfully submit that the surprising and superior results described by Dr. Giese further demonstrate the patentability of the instantly claimed molecules. Accordingly, withdrawal of the rejection respectfully is requested.

J. The rejection is based on a misapplication of the law

The Examiner admits that neither of the cited references describe the claimed dsRNA molecules and, more specifically, admits that neither references teaches or suggests dsRNA molecules containing an alternating pattern of 2'-O-Me modified and unmodified RNA nucleotides on both strands, where the strands are arranged as set forth in the claims. Nevertheless, the Examiner bases the rejection on the notion that McSwiggen and Tuschl teach that modification of some number of unidentified nucleotides in unidentified positions (as in McSwiggen) or at the terminus of the strands (as in Tuschl) renders obvious the instantly claimed molecules because the claimed molecules could be obtained by "routine experimentation," citing *In re Aller* in support of this proposition. Applicants respectfully traverse because the grounds for the rejection are contrary to the express language of 35 USC §103, and ignore the express instructions laid down in the MPEP regarding this type of rejection.

The express language of 35 USC 103 provides that "patentability shall not be negatived by the manner in which the invention was made." This language in the statute was inserted to make it clear that inventions are fully patentable even though they arise from routine research and development programs involving typical trial and error methods. The CCPA made it plain that rejections that rely on the notion that an invention is obvious merely because it could have been obtained by routine experimentation are contrary to law ("the emphasis upon routine experimentation is contrary to the last sentence of section 103," *In re Yates*, 211 USPQ 1149 (CCPA)). Accordingly, withdrawal of the rejection respectfully is requested.

The MPEP sets forth the very limited and specific types of situation in which an invention may be rejected as obvious based upon the notion of routine experimentation. See MPEP 2144.05. Notably, the instantly claimed invention does not remotely resemble the type of situation contemplated in the MPEP or in *In re Aller,* relied on by the Examiner. Thus the MPEP

states that the type of rejection sustained in *Aller* applies to ranges of common reaction variables such as concentration or temperature. Se MPEP 2144.05.II.A. Nowhere, either in the MPEP or in the case law, is there a single case standing for the proposition that *changes in chemical structure* are obvious because they allegedly could be arrived at by "routine experimentation." Indeed, if it were otherwise, no patents on new pharmaceuticals would issue, since the unpredictable relationship between chemical structure and biological activity requires progress through trial and error and variation and substitution of functional groups in a manner that the Examiner deems "routine experimentation." For at least these reasons, the basis for the rejection that the claimed structures were merely optimized positions arrived at by routine experimentation is improper and should be withdrawn.

Cook, Damha and Tuschl

Cook is cited as teaching "gapmer" antisense oligonucleotides containing 2'-modified nucleotides where each nucleotide can be linked with phosphodiester bonds. The Examiner cites Cook as teaching that substitution at the 2' position increased binding affinity and enhanced activity. Damha is cited as teaching antisense oligonucleotides with alternating modified and unmodified nucleotides where unmodified deoxyribonucleotide alternates with a 2'-modified nucleotide and that the nucleotides can be linked with phosphodiester bonds.

The Examiner admits that Tuschl does not teach an siRNA having alternating 2' modified and unmodified oligonucleotides, but asserts that Tuschl recognizes that certain chemical modifications of the 2'-OH result in enhanced nuclease resistance as well as modulation of RNAi activity. Based upon these alleged facts, the Examiner asserts that it would have been obvious to make a dsRNA molecule comprising 2'-modified nucleotides, as taught by Tuschl and it would have been "a matter of routine experimentation to use the general conditions of incorporating alternating segments of modified and unmodified nucleotides, as taught by Cook et al. and Damha et al. to discover the optimal number and placement of 2'-modifications in any dsRNA molecule, such that the resulting dsRNA molecule was endowed with maximum stability and functionality." Applicants respectfully traverse.

Damha is not available as prior art

Damha was not published until after the filing date of the instant application but has a claimed priority date of February 1, 2002. Accordingly, Damha is available as a reference only under 35 USC § 102(e) and may properly be antedated by an appropriate evidentiary showing of prior invention. The accompanying declaration by the inventors clearly demonstrates that the captioned application was reduced to practice prior to February 1, 2002, the earliest effective filing date of Damha . Accordingly, Damha is not available as a reference, and the rejection must stand or fall on the combination of Cook and Tuschl. In any event, for the reasons set forth herein, even if Damha were available, the cited references fail to teach or suggest the instantly claimed invention and the rejection should be withdrawn.

Cook teaches away from the claimed invention

Cook is limited to single stranded antisense molecules but, in any event, fails to teach modification to the inner region of the RNA molecule that is responsible for activity. In fact, Cook specifically states that internal modifications to the RNA using 2'-O-methyl groups inactivate the antisense molecule (column 16, Table 1). The molecules of the present invention necessarily have modifications that span the center of the molecule, on both strands. However, one of ordinary skill in the art, reading Cook, would learn to avoid making modifications in the center of an oligonucleotide, lest the molecule be inactive. Accordingly, Cook directly teaches away from the instantly claimed invention, and the rejection is improper and should be withdrawn.

Damha also teaches away from the claimed invention

Damha is cited as teaching antisense oligonucleotides with alternating modified and unmodified nucleotides where unmodified deoxyribonucleotide alternates with a 2'-modified nucleotide and that the nucleotides can be linked with phosphodiester bonds. The Examiner asserts "Damha et al. unexpectedly discovered antisense oligonucleotides consisting of this pattern of alternating segments of modified and unmodified nucleotides were able to elicit gene inhibition more efficiently than antisense oligonucleotides without this alternating pattern." The Examiner however, leaves out two important facts.

First, Damha does not teach the unexpected results using 2'-O-methyl modifications. The unexpected results of Damha were the result of a different chemical modification (an isomeric form of the ribose sugar) to a different nucleic acid (DNA rather than RNA). Specifically, Damha's molecules are single stranded molecules containing alternating *deoxy*ribonucleotides and *arabo*nucleotides.

Second, Damha does describe alternating 2'-O-methyl modification of antisense molecules, but these molecules "showed only poor ability to elicit RNase H degradation of target RNA" (paragraph [0149] and Figure 3). Thus, rather than showing unexpectedly good results, the 2'-O-methyl modified nucleic acid of Damha showed poor results. Accordingly, Damha directly teaches away from the instantly claimed invention, and the rejection is improper and should be withdrawn.

The combination of Cook and Tuschl fails to teach or suggest the claimed invention

For the reasons described above, Damha is not available as a reference and therefore the rejection must stand or fall on the combination of Cook, which teaches away from the claimed invention, and Tuschl, whose deficiencies are discussed in detail above. Here, Tuschl is cited as teaching dsRNA capable of mediating interference of gene expression and also as teaching that siRNA comprising minimal 2'-O-modifications retain RNAi activity and that modification of the entire double stranded RNA with 2'-O-methyl or 2'-deoxy is not well tolerated. However, as discussed in detail above, the only 2'-O-methyl modified dsRNA made by Tuschl was not only not well tolerated, but was inactive. In this fashion, Tuschl can also be considered as teaching away from the claimed invention in that the only 2'-O-methyl modified molecules described by Tuschl, in which the modifications spanned the center section of the molecule, were inactive. One of ordinary skill in the art would consider this as mere further proof of the teachings of Cook and Damha that 2'-O-methyl modifications to the center of the molecule should be avoided if activity is to be retained.

The Examiner again asserts that one would have been motivated to test "all possibilities and configurations" of 2'-O-modified and unmodified nucleotides because it was "well known" that this would impart increased stability and functionality in "any inhibitor nucleotides, such as a dsRNA." As addressed above, this assertion lacks any basis in fact and is contradicted by the

teachings of Tuschl, Cook. and Damha which all show that 2'-O-methyl modification across the inner region of a nucleic acid results in loss of activity.

The Examiner concludes that because Tuschl shows that a dsRNA having eight 2' modified nucleotides had RNAi activity while a fully 2'-O-methyl modified dsRNA abolished RNAi activity one skilled in the art would have been motivated to "search for the optimum number and placement of the 2' modifications in this range by routine experimentation to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA." Applicants submit that while Tuschl may demonstrate dsRNA with eight 2'-deoxy modified nucleotides had RNAi activity, the only 2'-O-methyl modified dsRNA tested by Tuschl was inactive. Moreover, far from providing motivation, Tuschl's "siRNA User Guide" warns against making 2'-O-methyl modifications to the inner region of the dsRNA.

The Examiner repeats the argument made in the rejection over McSwiggen and Tuschl that there were "a finite number of identified and predictable configurations of 2' modified and unmodified nucleotides such that one of ordinary skill in the art would have been motivated to incorporate such patterns of modifications with a reasonable expectation of success and it would have been routine to one of skill in the art to test these known patterns of modifications to identify a dsRNA with increased stability and functionality." Applicants again assert that there is no teaching in the cited references of any pattern of 2'-O-methyl modified dsRNA and no teaching of any nucleic acid with 2'-O-methyl modifications across a functional strand with increased stability and retained functionality. In light of the lack of guidance as to the relationship between 2'-O-methyl chemical modification and functionality, including the lack of guidance as to the placements of 2'-O-methyl chemical modifications based on the position of a nucleoside in a dsRNA there could be no motivation and no reasonable expectation of successfully making the claimed nucleic acid.

Moreover, for the reasons set forth in the Giese declaration, the instantly claimed molecules are both unexpectedly active in promoting gene silencing and also unexpectedly stable. For at least these reasons, applicants respectfully submit that the rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,

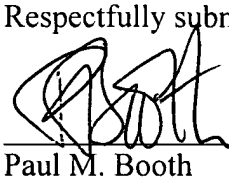

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EXHIBIT A